ORIGINAL RESEARCH PAPER

Forensic Medicine

TRAUMA, THE TRIGGERING FACTOR OF HEPATO-RENAL SYNDROME DUE TO MYOGLOBIN TOXICITY

KEY WORDS: Rhabdomyolysis; acute kidney injury; myoglobinuria; creatine kinase; epilepsy

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ABSTRACT

Background: Myoglobin**,** essentially acytoplasmic hemoprotein in striated muscle, expressed solely in cardiac myocytes and oxidative skeletal muscle fibers. The heme residue binds the oxygen reversibly by a porphyrin ring - iron ion complex. Functionally, myoglobin is an oxygen storage protein in muscle, capable of releasing oxygen during hypoxia or anoxia. Apart from this myoglobin provides additional function like scavenging nitric oxide and reactive oxygen species, thus acts like an antioxidant. Myoglobin toxicity is not uncommon with trauma and degenerative muscle pathology. This involves a condition commonly called rhabdomyolysis, which results when the skeletal muscle gets damage due to strenuous exercise. In majority of cases it is self limiting but when there is intense damage, the muscle proteins gets released into the circulation and gets deposited in the renal tubules resulting in acute tubular necrosis, with subsequent acute renal failure. From the literature survey it is evident that, a high proportion of marathon runners had developed acute rhabdomyolysis. Azotemia, severe metabolic acidosis, disseminated intravascular coagulation and acute liver failure results due to rhabdomyolysis go unnoticed.

Methods: A series of cases who succumbed due to rhabdomyolysis due to various etiology were studied after taking the consent. A detailed analysis of cases and the autopsy findings were noted and tabulated in the table 1. Clinical correlation of the pathophysiology of hepato-renal syndrome was studied with respect to rhabdomyolysis.

Results: As per the table 1 and figures 1-11

Conclusion: Early detection and hemodialysis will be helpful in unnoticed fatal acute tubular necrosis due to rhabdomyolysis. Not only marathon runners suffer muscle damage but also epilepsy and trauma suffer. apart from treating the primary pathology rhabdomyolysis has to be identified and treated promptly.

Introduction:

Myoglobin, essentially acytoplasmic hemoprotein in striated muscle, expressed solely in cardiac myocytes and oxidative skeletal muscle fibers. The heme residue binds the oxygen reversibly by a porphyrin ring - iron ion complex. Functionally, myoglobin is an oxygen storage protein in muscle, capable of releasing oxygen during hypoxia or anoxia. Apart from this myoglobin provides additional function like scavenging nitric oxide and reactive oxygen species, thus acts like an antioxidant. Garry et al.[1] provides a concise account of the genomic organization and transcriptional regulation of myoglobin and also reveals that the expressed concentration of myoglobin increases with the increase in activity and increases dramatically in oxidative, fatigue-resistant fibers.[2] Neonatal dolphins, penguins and seals have myoglobin levels in locomotor muscles that are a fraction of those seen in adults.[3] As the young mature and spend increasing amounts of time swimming and diving, myoglobin content in their muscles increases accordingly, approaching adult levels. Thus, although genetics plays an important role in establishing inherent levels of muscle myoglobin content, developmental programs and/or environmental cues and stresses such as physical activity, temperature and oxygen availability play at least equally important roles in determining functional levels of this protein.

In humans post-traumatic and post-stress concentration of myoglobin plays a dominant role in mortality and morbidity which usually go un-noticed. Death as investigated by Forensic expert will have significant medico-legal ramifications in addition to providing valuable information to the medical fraternity, deceased's family and community as a whole. In case of strenuous exercise, rapid rigorous contraction and relaxation of skeletal muscles, as in epilepsy and status epilepticus,physical torture andskeletal muscle degeneration, the muscle enzyme leakage occurs resulting in life threatening syndrome, exertional rhabdomyolysis. The muscle cells get damaged and there will be rapid release of muscle enzyme and other cellular enzymes which has been reported by various authors in cases of athletes, skiing, and marathon running, rowing etc which involves strenuous exercises.[4]The release of muscle cell enzyme, myoglobin into blood circulation results in myoglobinemia which is excreted in urine, myoglobinuria,[5] and acute kidney injury occurs in such, progressing to acute renal failure in about 5% to 7%.[6] Apart from the routine measurement of urine output, blood urea, serum creatinine, blood urea nitrogen, and other renal parameters, the color of urine and measurement of myoglobinuria, and liver function tests in cases of trauma plays a dominant role in early diagnosis of rhabdomyolysis. The treating doctor should consider the change in color of urine in such cases at the initial stage itself so that an actual diagnosis can be made in the golden hour. A quick diagnosis is expected in rhabdomyolysis, as it is uncommon and mostly affects productive age group,[7] and the pathogenesis of rhabdomyolysis progresses rapidly to mortality with the involvement of renaland hepato-biliary system. Here we present a case series of such cases where there was an impediment in diagnosis and the cases succumbed.

1. Data collection

1.1. Case summary 1

An apparently healthy well-built and nourished, 24year old male while posted to commando training, ran for 15-20km/day for 4 consecutive days as a part of training. On the 5th day he collapsed with history of fatigue and weakness. The person was advised bed rest and later after 24hours presented to emergency department with disorientation, afebrile, pulse rate 66, low volume, regular with normal vessel wall and blood pressure 110/70mmHg. All the organs systems were normal. The person succumbed with a survival period of less than 24hours. No history of any drug abuse such as cocaine, amphetamines, statins, heroin etc. The significant ante-mortem biochemical parameters were as follows;

- Blood Urea- 167 (from the sample taken as soon as the patient arrived to Emergency department) and 188 (from the sample collected after 3hr)
- S Creatinine- 6.9 (from the sample taken as soon as the patient arrived to Emergency department) and 7.2 (from the sample collected after 3hr)
- Na^+ 143meq/l
- K^- 6.3meq/l
- ALT- 600u/dl
- AST- 876u/dl
- PT, APTT-Prolonged

- Myoglobinuria- not done
- ECG- Normal Post-mortem Clinical Forensic investigation of urine (sample collected from the urinary bladder within 3hours after death)
- Specific gravity- 1.030
- Blood- 4+
- RBC 8-10/HPF
- WBC 6-8/HPF
- Protein- 2+
- Glucose- Nil
- Ketone bodies- Nil
- Urine myoglobin-390 (A normal urine sample does not have myoglobin)

1.2. Case summary 2:

An 18year old male with status epileptics, brought to the emergency and was treated promptly for the same. The person was already in disoriented condition and was sedated as a part of epilepsy treatment. The treating doctor was considering only the existing pathology and later the case succumbed.

The significant parameters were as follows;

- Blood Urea- 117
- S Creatinine- 4.2
- Na^+ 136meq/l
- K^- 5.1meq/l
- ALT- 570u/dl
- AST- 746u/dl
- Myoglobinuria- not done
- ECG- Normal

1.3. Case summary 3

A 16year old male was tied to a chair and was hit by parents by a wooden ruler of 2cm diameter below the hip and below the shoulder for recurrent failing in academics. Apart from passing dark to cola colored urine after 24-48hours there was no significant history. After 72hoursthe boy succumbed and was brought dead. No bio-chemical parameters could be availed.

All the three cases were subjected to post-mortem examination. The post-mortem was conducted at Department of Forensic Medicine and Toxicology, Jawaharlal Nehru Medical College, Belgaum and District Hospital, Chamarajanagar, Karnataka, India. The findings were tabulated. (Table 1) The images produced were taken after washing the viscera in running water.

2. Discussion:

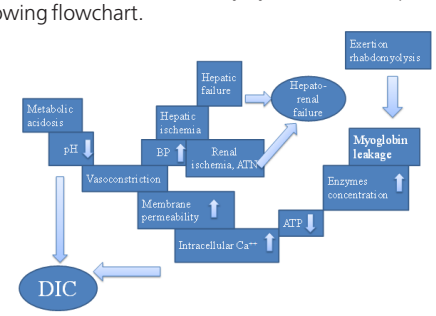
Rhabdomyolysis literally means, "dissolution of skeletal muscle". It is a syndrome involving injury to skeletal muscle which results in leakage of potentially toxic intracellular components into the plasma,[8] first described in the victims of crush injury during World War II.[9]Rhabdomyolysis can present solitarily or as a complication of trauma, and severe physical exercise or physical torture. In rare instances it can be due to hereditary, metabolic or structural abnormalities of the skeletal muscle cells.[10] The basic pathology in rhabdomyolysis lies in the disturbance of myocyte calcium homeostasis and accompanied myoglobinuria due to release of muscle protein, creatine phosphokinase and myoglobin, as a part of damage to sarcolemma. The fatality in rhabdomyolysis is due to fatal complications like acute renal failure, hyperkalemia, cardiac arrest, disseminated intravascular coagulation and compartment syndrome.[11, 12] Thus rhabdomyolysis has a broad spectrum of presentation from benign asymptomatic to malignant fatal condition. In the midst of clinical features it is acute kidney injury, the most significant complication. Prompt recognition and management of rhabdomyolysis is crucial in preserving renal function. Microscopic myoglobinuria in the absence of obvious trauma is the pathgnomonic feature of acute renal failure and hypercalcimia during dieresis, may be exclusive of acute renal failure due to rhabdomyolysis. It is very essentialto prevent acute renal failure in managing a case of rhabdomyolysis.A 4-5 fold rise in serum creatine phosphokinase level is the sensitive marker of myocyte injury.[13] Highly increased creatine phosphokinase is related to rise in serum creatinine and subsequently renal failure.[14]It is essential to draw a clear line between physiological response and exertional rhabdomyolysis in relation to rise in the level of serum creatine kinase after exercise.

In the present case series it is trauma and muscle compression are the cause of rhabdomyolysis through direct injury to muscle. Indirectly vessel occlusion causing ischemia due to thromboemboli, traumatic injury, has lead to rhabdomyolysis. This is the most similar to a review which reveals that the leading cause of rhabdomyolysis in children of 9-18 years of age.[15]Other significant etiologic factors like orthopedic injuries, blunt trauma, shaken-baby syndrome, physical abuse,[16, 17] high-voltage electrical injury due to lightning or accidental electrocution,[18] heat stroke, extensive burns, near-drowning, prolonged immobilization after excess alcohol or drug consumption, after an un-witnessed incapacitating stroke or seizure, or after prolonged surgical procedures compounded by hypovolemia, hypoxemia can significantly increase the incidence of rhabdomyolysis. Drugs like opium, alcohol and tramadol[19,20]and myotoxins can impair skeletal muscle ATP production or drug-induced sarcolemmal injury often mediated by phospholipase A activation cause rhabdomyolysis.[21] Gokel described two cases with rhabdomyolysis induced acute renal failure complicating by monocrotophos poisoning associated with subarachnoid hemorrhage.[22] Cairns RS tried to illustrate the concept that the possibility of transient hypovolemic exercise-associated hyponatremia may precede and augment creatine phosphokinase during an ultramarathon[23]which was not observed in the present scenario. Hypokalemia due to excessive sweating along with hyponatremia can impair normal muscle physiology was not observed, however hyperkalemia was observed in Case 1 and 2 which signifies renal failure.

As per National institutes of health, Web MD, exercise is good to maintain health. When it is beyond the normal limit it can result in general feeling of malaise, fatigue, painful movement of joints, nausea, vomiting, fever, confusion, disorientation, loss of consciousness and abnormal irregular heart beat. In such vague clinical presentation the treating physician should be careful in analyzing. But when there is history of trauma in combination with muscle pain or cramping with history of passing dark colored urine it is mandatory to rule out myoglobinuria and the possibility of exertional rhabdomyolysis not mere cardio-respiratory arrest as the cause of death.When there is associated significant electrolyte abnormalities patients may present with cardiac arrhythmias and arrest.

In the present scenario we present case series with myoglobinuria resulted from strenuous exercise, seizures, prolonged coma, a marker of rhabdomyolysis in traumatic or non-traumatic etiology was the sole identifiable explanation for acute renal failure associated with hepato-cellular failure can be the cause of sudden death. These cases with microscopic hematuria occurring in runner and collapsed while running, and due to status epileptics with presence of dark-colored urine dismissed initially. These clinching clinical features when unnoticed result in unfavorable outcomes. In such cases if it is associated with myoglobinuria it is capable of causing hepato-renal failure, a potent cause of death. Incidence of hepato-renal syndrome annually ranges between 8% and 40% in acute exertional rhabdomyolysis.[24]Landau et al[25] revealed that excessive, prolonged or repetitive over stretch of the sarcoplasmic reticulum results in increase calcium influx which activates sarcolemma and degrading enzymes. As a result of this the permeability of the sarcolemma alters causing release of harmful proteins to blood potentially leading to acute renal failure, variation in clotting system and arrhythmias.

The summarized forensic-patho-physiology of hepato-renal syndrome in acute rhabdomyolysis can be depicted as in the following flowchart.



Flow chart: Forensic-patho-physiology of hepato-renal syndrome in acute exertional rhabdomyolysis

In all the presented cases the cause of sudden death was hepato-renal syndrome and disseminated intravascular coagulation in rhabdomyolysis. McMahon et al developed a risk scoring system for predicting renal failure or death in rhabdomyolysis. This scoring system involves age, sex and exercise, biochemical parameters like serum creatinine, calcium, creatinine phosphokinase, phosphate and bicarbonate level, and initiation of clinical features like seizures, syncope and myositis. These components for scoring are derived as follows;

- Age (50-70 years, 1.5 points; 71-80, 2.5 points; >80, 3 points)
- Female sex (1 point)
- Initial creatinine level (1.4-2.2 mg/dL, 1.5 points; >2.2 mg/dL, 3 points)
- Initial calcium level (< 7.5 mg/dL, 2 points)
- Initial CPK level (>40,000 U/L, 2 points)
- Origin not seizures, syncope, exercise, statins, or myositis (3 points)
- Initial phosphate level (4.0-5.4 mg/dL, 1.5 points; >5.4 mg/dL, 3 points)
- Initial bicarbonate level (< 19 mEq/L, 2 points)

The risk of death or renal failure was 3% in patients with a score lower than 5 and 59.2% in patients with a score higher than 10.[26]Hypoxia and oxidative stress play a major role in pathogenesis. Fruitful results can be expected if the early features of ischemia, mainly hepatic ischemia are identified. Congestion was prominent in Case 2 where as pallor was prominent in Case 1 illustrates that there was predominant hypoxemia. In Case 2 and in Case 1 there was both hypoxemia and bleeding which were vicious in nature.

3. Conclusion

Myoglobinuria-Rhabdomyolysis will continue to be an important factor and should be considered in all cases of trauma, torture, non-acute hepato-renal syndrome and unexpected deaths particularly in post-trauma and stress or in presence of myoglobinuria and increase creatine phosphokinase. Clinicians as well as forensic pathologists should be aware of the fact that mere cardio-respiratory arrest can virtually masquerade the patho-physiology of any disease and hence the clinical features in relation to myoglobinuria-rhabdomyolysis should be given due significance in ante-mortem as well as post-mortem diagnosis.

Table 1: Salient features

	Case 1	Case 2	Case 3
Ante-mortem features			
Symptoms duration (days)	history of fatigue and weakness, 2-3days	history of generalized toic clonic seizures, 2-3days	2 days back he was beaten
Disorientation	1day	2days	Case was brought dead
Weakness and fatigue	2days	-	-
Discharges	-	Present in the form of tonic-clonic seizures	-
Post-mortem features			
External examination	- No injuries - Yellowish discoloration of both sclera - Subconjunctival hemorrhage on the right eye - Extravasation of blood in submucosa of lips and subcutaneous tissue in thigh and iliac region (Fig 1 and 2)	- No injuries - Tongue bite	- Multiple faint bluish-black 'train track' contusions - Multiple paticheal hemorrhage (Fig 1)
Internal examination	- Sub-mucosal hemorrhage - Sub-cutaneous and intra-muscular hemorrhage - Sub-mucosal bleeding around the larynx and inside the trachea - Hemorrhagic spots in lungs - Subendocardial hemorrhage - Internal bleed in the mucosa of stomach, into the omentum and the mesentery - All organs were congested - Loss of normal cortico-medullary architecture (Fig 3-9)	- Brain edematous and congested - Hemorrhagic spots in lungs - Loss of normal cortico-medullary architecture in kidney - All organs were congested	- All organs were congested - Loss of normal cortico-medullary architecture of kidney (Fig 9)
	On catheterization 120ml of dark colored urine got collected in the uro- sac.(Fig 10)	80ml of urine collected from the bladder	140ml of urine collected from the bladder

5. Images

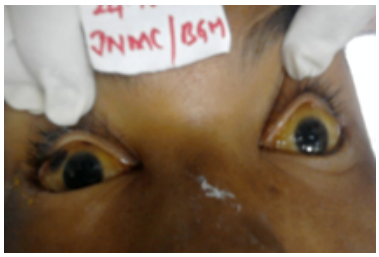


Fig 1: Yellowish discoloration of both sclera and subconjunctival hemorrhage on the right eye (Case 1)

Case 1	Case 1	Case 3

Fig 2: Sub-mucosal bleeding in the lower lip, on the outer surface of the upper part of the right thigh and patechial hemorrhage in both the legs

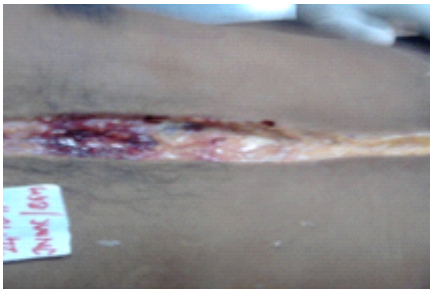


Fig 3: Intra-muscular hemorrhage found in the mid-line incision (Case 1)

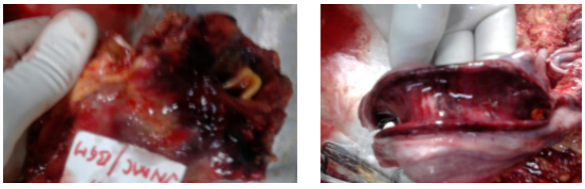
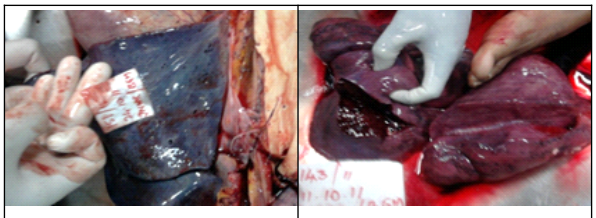
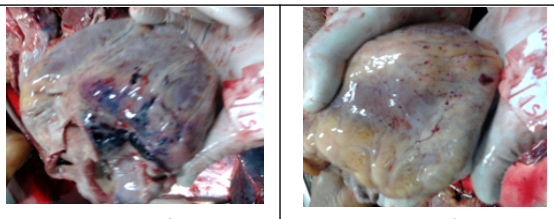


Fig 4: Sub-mucosal bleeding around the larynx (Case 1) and inside the trachea (Case 2)



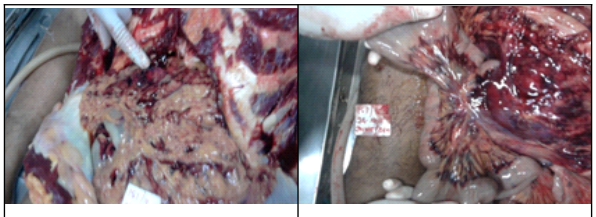
Case 1	Case 2

Fig 5: Hemorrhagic spots in lungs



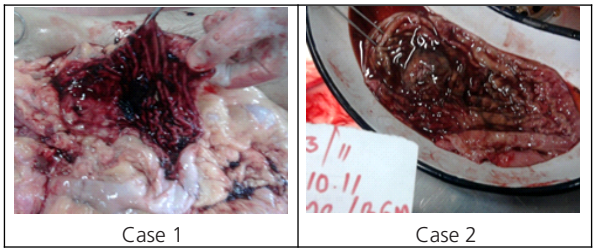
Ventral surface	Basal surface

Fig 6: Endocardial hemorrhage (Case 1)



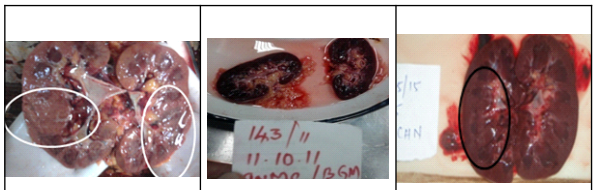
Case 1	Case 2

Fig 7: Internal bleed into the omentum and mesentery



Case 1	Case 2

Fig 8: Internal mucosal bleed inside the stomach



Case 1	Case 1	Case 3

Fig 9: Loss of normal cortico-medullary architecture (Case 1 and 2) and severe congestion in Case 2

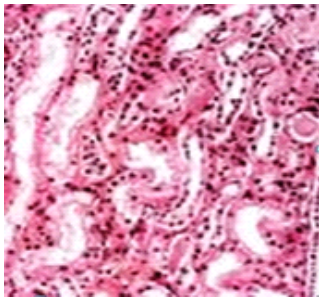


Fig 10: Focal loss of tubular epithelial cells in Case 1stained with hematoxylin and eosin.

Urine sample

Fig 11: Dark colored urine collected in the uro-sac compared with normal straw yellow colored urine.

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